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## ORIGINAL ARTICLE

# Novel insights into the epidemiology of epidermolysis bullosa (EB) from the Dutch EB Registry: EB more common than previously assumed?

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## Abstract

**Background** Epidermolysis bullosa (EB) is a heterogeneous group of rare and incurable genetic disorders characterized by fragility of the skin and mucosae, resulting in blisters and erosions. Several epidemiological studies in other populations have been carried out, reporting varying and sometimes inconclusive figures, highlighting the need for standardized epidemiological analyses in well-characterized cohorts.

**Objectives** To evaluate the epidemiological data on EB in the Netherlands, extracted from the molecularly well-characterized cohort in the Dutch EB Registry.

**Methods** In this observational study all EB-patients that were based in the Netherlands and captured in the Dutch EB Registry between 1988 and 2018 were included. The epidemiological outcomes were based on complete diagnostic data (clinical features, immunofluorescence, electron microscopy and mutation analysis), with longitudinal follow-up.

**Results** A total of 464 EB-patients (287 families) were included. The incidence and point-prevalence of EB in the Netherlands were 41.3 per million live births and 22.4 per million population, respectively. EB Simplex (EBS), Junctional EB (JEB), Dystrophic EB (DEB) and Kindler EB were diagnosed in 45.7%, 18.8%, 34.7% and 0.9% of the EB-patients, respectively, with an incidence and point-prevalence of 17.5 and 11.9 (EBS), 9.3 and 2.1 (JEB), 14.1 and 8.3 (DEB), 0.5 and 0.2 (Kindler EB). In 90.5% of the EB-patients the diagnosis was genetically confirmed. During the investigated time period 73 EB-patients died, 72.6% of whom as a direct consequence of their EB.

**Conclusion** The epidemiological outcomes of EB in the Netherlands are high, attributed to a high detection rate in a well-organized set-up, indicating that EB might be more common than previously assumed. These epidemiological data help to understand the extensive need for (specialized) medical care of EB-patients and is invaluable for the design and execution of therapeutic trials. This study emphasizes the importance of thorough reporting systems and registries worldwide.

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## Conflict of interest

None.

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## Introduction

Epidermolysis bullosa (EB) is a heterogeneous group of rare and incurable genetic cutaneous disorders, caused by mutations

within the genes encoding critical proteins for the intra-epidermal cell–cell adhesion and dermo-epidermal junction (DEJ).<sup>1,2</sup> The very recent consensus classification has now divided this heterogeneous group of skin fragility disorders in ‘classical’ EB and ‘EB-related’ disorders.<sup>2</sup> Depending on the level of skin cleavage, four major types of EB are recognized: EB Simplex (EBS),

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<sup>‡</sup>Both authors contributed equally and are to be considered as joint first authors.

Junctional EB (JEB), Dystrophic EB (DEB) and Kindler EB. Based on the clinical severity, inheritance pattern and molecular defects, these major types of EB are further divided into many subtypes, that share common features of mechanical fragility and blistering of the skin and mucous membranes.<sup>1,2</sup> Most EB-patients have lifelong blistering and erosions with significant morbidity due to related complications, associated with early mortality.<sup>1</sup>

The Center for Blistering Diseases at the University Medical Center Groningen (UMCG) in the Netherlands is a recognized European and the only national expertise centre for EB. Since the registration of its first patient in the Dutch EB Registry (Dutch-EB-Reg) in 1988 the centre has evolved and contributed to the diagnosis, research and management of EB-patients in the Netherlands and other countries for over three decades.<sup>3</sup>

Epidemiological data improve our understanding of EB, emphasize the extent and need for (specialized) medical care of EB-patients and are invaluable for the design and execution of therapeutic trials. Several epidemiological studies in other populations have been carried out, reporting varying and sometimes inconclusive figures (incidences of 1.4–25.0 per million live births and prevalences of 2.82–54.0 per million population), mostly based on clinical features or molecular findings. Through this report, we provide accurate epidemiological figures of each subtype of EB according to the novel consensus report, including subtype-specific mortality rates, extracted from the molecularly well-characterized Dutch EB cohort in the Dutch-EB-Reg, established over a 31-year period.

## Materials and methods

### Study design and data collection

In this population-based and observational (cross-sectional and longitudinal) study, all EB-patients registered at our centre from 01-Jan-1988 until 31-Dec-2018 were included. EB-patients referred to our expertise centre by specialists from foreign countries were excluded in order to provide accurate epidemiological outcomes of EB in the Netherlands. The diagnosis of EB was established based on clinical features, skin biopsies for immunofluorescence antigen mapping (IFM) and transmission electron microscopy (TEM), and in particular mutation analysis, which over the years evolved from sanger sequencing of single candidate genes to next-generation sequencing of multiple EB-related genes in parallel.<sup>4</sup> The subclassification of EB was conducted according to the latest consensus report.<sup>2</sup> The medical records of the EB-patients were systematically collected during the investigated time period and retrospectively examined. This study was carried out in accordance with the principles of the Declaration of Helsinki.

### EB-related skin fragility disorders

The 2020 EB-consensus reclassification separated the former suprabasal EBS phenotypes as 'EB-related skin fragility

disorders' from the classical EB-phenotypes (acral peeling skin syndrome, lethal acantholytic EB, skin fragility-woolly hair syndrome and skin fragility-ectodermal dysplasia syndrome).<sup>1,2</sup> Therefore, patients with such phenotypes were excluded in the calculations and described in the Appendix S1 (Supporting Information).

### Data analysis

The quantitative and qualitative characteristics of the EB-patients were summarized as absolute numbers, averages together with standard deviations (SD) and proportions (%). Incidences were calculated per million live births [total no. of new EB-patients born (1-Jan-1988 until 31-Dec-2018)/total no. of live births (1988–2018)\*1 000 000], when calculated per year the incidences were presented as rates. Prevalences were calculated per million population [total no. of EB-patients alive at a time point (31-Dec-2018)/total population at a time point (31-Dec-2018)\*1 000 000]. The number of live births, average life expectancy of the Dutch population and population size of the Netherlands were collected from the national Central Agency for Statistics (<https://opendata.cbs.nl/#/CBS/nl/>). The epidemiological data were analysed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). There was no correction for multiplicity.

## Results

### Incidence and point-prevalence

From 1 January 1988 until 31 December 2018, 544 EB-patients (358 families) were registered at our centre, of which 80 EB-patients (71 families; 14.7%) referred by specialists from foreign countries. The remaining 464 EB-patients (287 families; 247 males and 217 females) were based in the Netherlands, of which 346 patients were of Dutch descent (74.6%), 27 patients had a mixed ethnic background (5.8%), 78 patients were immigrants (16.8%) ( $n = 13$  unknown, 2.8%). The incidence and point-prevalence of EB in the Netherlands were calculated to be 41.3 per million live births (5 830 469 live births, 1988–2018, StatLine, CBS, The Hague, (South Holland), Netherlands) and 22.4 per million population (17 282 163 total population, 31-Dec-2018, StatLine, CBS).

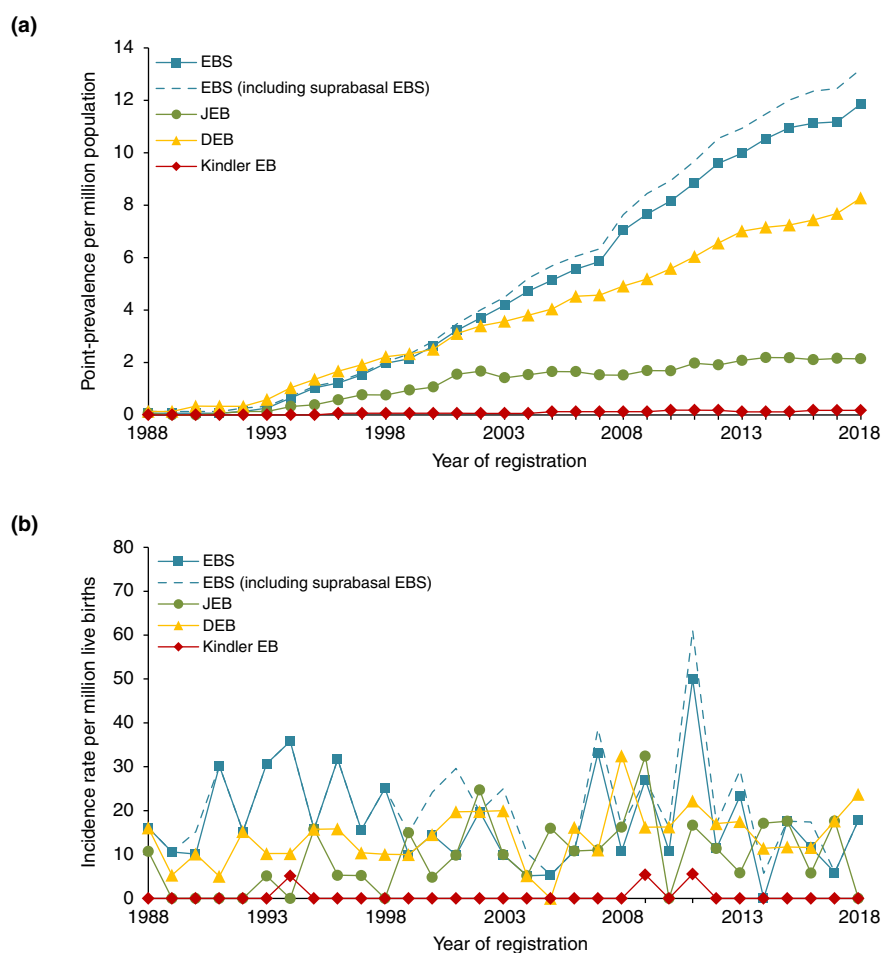
Overall, a genetic diagnosis was made in 420 patients (254 families; 90.5%). In 22 patients (18 families; 4.7%) no DNA was available for mutation analysis. In another 22 patients (15 families; 4.7%) no pathogenic mutation could be found (or just a single pathogenic mutation in case of recessive EB) and hence classified as genetically unsolved (Fig. 2b). However, the level of blister formation could be established by IFM and TEM on available skin biopsies in most of these patients, and therefore the major type of EB ( $n = 10$  unknown).<sup>4</sup> Dominant inheritance was present in 304 patients (149 families; 65.5%) and recessive inheritance in 160 patients (138 families; 34.5%). Only in 16 patients with recessive EB it remained uncertain whether the parents were consanguineous or not.

**EB simplex** In the Dutch-EB-Reg, EBS was most frequently diagnosed (212 patients; 108 families; 45.7%) with an incidence of 17.5 per million live births and a point-prevalence of 11.9 per million population (Figs. 1 and 2a, Table 1). Dominant EBS was more common than recessive EBS (191 patients; 94 families; 90.1% vs. 21 patients; 14 families; 9.9%). In 81.0% of the patients with recessive EBS a homozygous mutation was found, of which 52.9% associated with known parental consanguinity. Mutation analysis implicated six genes in the EBS cohort. In 8.5% of the EBS-patients ( $n = 18$ ) the causative gene could not be discovered.

**Junctional EB** Junctional EB was diagnosed in 87 patients (72 families; 18.8%) with an incidence of 9.3 per million live births and a point-prevalence of 2.1 per million population (Figs. 1

and 2a, Table 2). JEB was inherited autosomal recessively in 94.3% of the cases, of which 43.9% carried a homozygous mutation (of which 58.3% associated with known parental consanguinity). In five patients (one family; 5.7%) a dominant form of JEB was diagnosed, with a mutation in the *ITGB4* gene.<sup>5</sup> Six genes were implicated in the pathogenesis of JEB in our cohort. In 13.8% of the JEB-patients ( $n = 12$ ) the diagnosis could not be confirmed genetically.

**Dystrophic EB** Dystrophic EB was identified in 161 patients (103 families; 34.7%) with recurrent and unique mutations in the *COL7A1* gene (Fig. 2a). An incidence of 14.1 per million live births was calculated and a point-prevalence of 8.3 per million population (Fig. 1, Table 3), with dominant DEB (DDEB) in 108 patients (54 families; 67.1%) and recessive DEB (RDEB) in

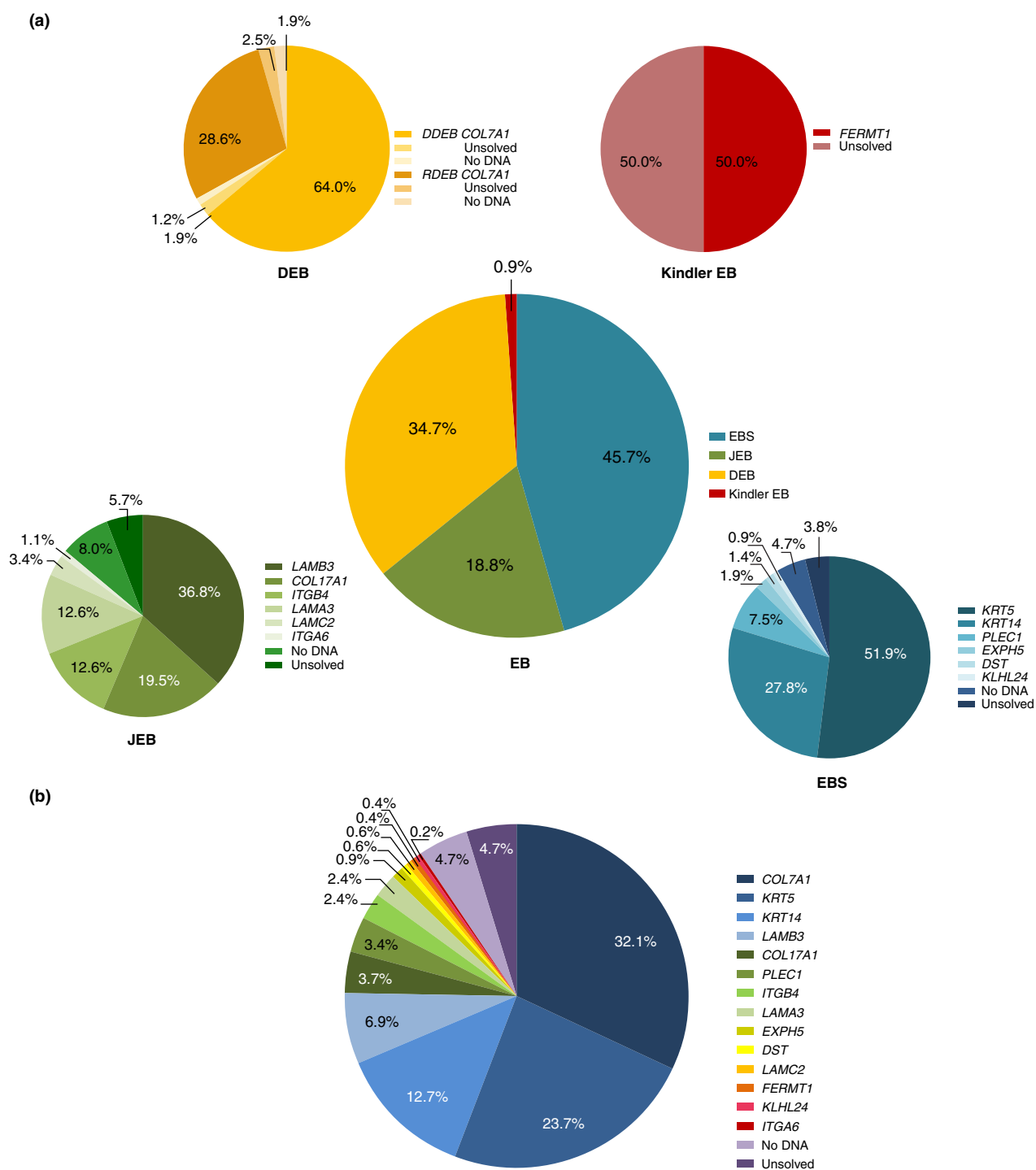


**Figure 1** Epidemiological outcomes of each major type of Epidermolysis Bullosa in the Netherlands for the time period 1988–2018,  $n = 490$ . (a) Annual point-prevalence (per million population) of each major type of EB. (b) Annual incidence rates (per million live births). Based on the Dutch Epidermolysis Bullosa Registry (Dutch-EB-Reg). DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; EBS, epidermolysis bullosa simplex; JEB, junctional epidermolysis bullosa.

**Table 1** Epidemiological data and distribution of Epidermolysis Bullosa Simplex in the Netherlands for the time period 1988–2018,  $n = 212$ ††† no mutation analysis was performed or pathogenic mutation(s) could be found, the patients were still included in the calculation of the incidence and point-prevalence for the concerned subtype of EBS. ‡ Incidence (per million live births) = total no. of new EBS-patients born (1988–2018)/total no. of live births (1988–2018)\*1 000 000. Total live births in the Netherlands from 01-Jan-1988 until 31-Dec-2018: 5 830 469 (StatLine, CBS). §Point-prevalence (per million population) = total no. of EBS-patients alive at a time point (31-Dec-2018)/population at a time point (31-Dec-2018)\*1 000 000. Total Dutch population, 31-Dec-2018: 17 282 163 (StatLine, CBS). ¶Two patients with EBS-localized, without mutation analysis performed, were included because a pathogenic mutation in *KRT5* was found in a family member, with a comparable clinical presentation. ††The group of 'Unsolved' EBS-patients consisted of the following:  $n = 7$  EBS-localized and  $n = 1$  EBS-intermediate. †††The group of 'No DNA' EBS-patients consisted of the following:  $n = 4$  EBS-localized,  $n = 3$  EBS-intermediate and  $n = 3$  EBS-severe.

EB type	Cleavage level	Inheritance	Subtype	Gene involved	No. of patients (families)	Average age of patients (alive) on 31-Dec-2018 (in years) <sup>†</sup>	Incidence <sup>‡</sup>		Point-prevalence <sup>§</sup>	
							Per gene	EBS subtype	Per gene	EBS subtype
EBS	Intra-epidermal	Dominant	Localized	<i>KRT5</i> <sup>‡</sup>	52 (26)	36.1	4.1	7.2	3.0	5.5
				<i>KRT14</i>	33 (16)	36.5	2.2		1.9	
	Intermediate	Ogna	mottled pigmentation	<i>KRT5</i>	19 (6)	27.2	1.7		1.0	
				<i>KRT14</i>	4 (3)	29.1	0.3		0.2	
				<i>KLHL24</i>	2 (1)	31.1	0.2	4.8	0.1	3.1
				<i>PLEC</i>	10 (6)	49.4	0.3		0.5	
				<i>KRT5</i>	17 (10)	26.9	1.9		1.0	
				<i>KRT5</i>	22 (7)	28.4	2.4		1.3	
				<i>KRT14</i>	14 (9)	31.0	1.5	4.3	0.8	2.3
	Unsolved <sup>¶</sup>	No DNA <sup>§</sup>	Recessive		8 (4)	-	-		-	
					10 (6)	-	-		-	
	Recessive	muscular dystrophy skin-only		<i>KRT14</i>	8 (4)	56.8	0.2		0.3	
				<i>EXPH5</i>	4 (4)	12.5	0.7		0.2	
				<i>DST</i>	3 (2)	30.3	0.2	1.2	0.2	1.0
				<i>PLEC</i>	5 (3)	40.4	0.2		0.2	
	Total EBS			<i>PLEC1a</i>	1 (1)	33.9	-		0.1	
					212 (108)	34.3 years	17.5		11.9	

EB, epidermolysis bullosa; JEB, junctional epidermolysis bullosa.



**Figure 2** Distribution of the major types and genes involved in patients with Epidermolysis Bullosa in the Dutch Epidermolysis Bullosa Registry for the time period 1988–2018,  $n = 464$ . (a) The total distribution and genes involved in the major EB types in the cohort of the Dutch Epidermolysis Bullosa Registry (Dutch-EB-Reg). (b) The total distribution of the 14 genes involved in the Dutch Epidermolysis Bullosa Registry (Dutch-EB-Reg). Patients without mutation analysis performed were classified as ‘No DNA’; patients in which no pathogenic mutation(s) could be found with mutation analysis were genetically classified as ‘Unsolved’.

**Table 2** Epidemiological data and distribution of Junctional Epidermolysis Bullosa in the Netherlands for the time period 1988–2018,  $n = 87$ †If no mutation analysis was performed or pathogenic mutation(s) could be found, the patients were still included in the calculation of the incidence and point-prevalence for the concerned subtype of JEB (two stillborn patients, an induced partus of a foetus and a patient who was born and has died before 1988, were excluded in the calculations of the incidence and point-prevalence, but included in the number of affected patients). ‡Incidence (per million live births) = total no. of new JEB-patients born (1988–2018)\*1 000 000. Total live births in the Netherlands from 01-Jan-1988 until 31-Dec-2018: 5 830 469 (StatLine, CBS). §Point-prevalence (per million population) = total no. of JEB-patients alive at a time point (31-Dec-2018)/population at a time point (31-Dec-2018)\*1 000 000. Total Dutch population, 31-Dec-2018: 17 282 163 (StatLine, CBS). ¶The group of 'Unsolved' JEB-patients consisted of the following:  $n = 3$  JEB-localized ( $n = 2$  one pathogenic mutation in *LAMA3*,  $n = 1$  one pathogenic mutation in *ITGB4*) and  $n = 2$  JEB-pyloric atresia ( $n = 1$  one pathogenic mutation in *ITGB4*, ††The group of 'No DNA' JEB-patients consisted of the following:  $n = 4$  JEB-severe,  $n = 2$  JEB-subtype unknown (two stillborn patients) and  $n = 1$  JEB-pyloric atresia.

EB type	Cleavage level	Inheritance	Subtype	Gene involved	No. of patients (families)	Average age of patients (alive) on 31-Dec-2018 (in years) <sup>†</sup>	Incidence <sup>1,2</sup> Per gene	JEB subtype	Point-prevalence <sup>1,3</sup> Per gene	JEB subtype
JEB	Lamina lucida	Dominant	Localized	<i>ITGB4</i>	5 (1)	23.3	0.5		0.3	
			Localized	<i>COL17A1</i>	3 (3)	25.4	0.3		0.2	
		Recessive	Localized	<i>ITGB4</i>	2 (2)	55.5	0.2		0.2	
				<i>LAMA3</i>	2 (2)	43.7	0.3	1.0	0.2	0.7
				<i>LAMB3</i>	2 (2)	21.1	0.2		0.1	
				<i>COL17A1</i>	12 (11)	42.8	0.5		0.5	
			Intermediate	<i>LAMB3</i>	8 (5)	13.7	0.7		0.2	
				<i>LAMA3</i>	7 (4)	31.9	0.3	1.5	0.2	0.9
				<i>ITGB4</i>	1 (1)	-	-		-	
			Severe	<i>LAMB3</i>	22 (20)	-	3.6		-	
				<i>LAMC2</i>	3 (2)	-	0.5	5.0	-	-
				<i>LAMA3</i>	2 (2)	-	0.3		-	
			Pyloric atresia	<i>ITGB4</i>	2 (2)	-	0.5	1.0	-	-
				<i>ITGA6</i>	1 (1)	-	0.2		-	
Total JEB			Late onset	<i>COL17A1</i>	2 (1)	38.5	-		0.1	
			Unknown		1 (1)	-	-		-	
			Unsolved <sup>4</sup>		5 (5)	-	-		-	
			No DNA <sup>5</sup>		7 (7)	-	-		-	
					87 (72)	33.0 years	9.3		2.1	

EB, epidermolysis bullosa; JEB, junctional epidermolysis bullosa.

**Table 3** Epidemiological data and distribution of Dystrophic Epidermolysis Bullosa in the Netherlands for the time period 1988–2018,  $n = 161$  †If no mutation analysis was performed or pathogenic mutation(s) could be found, the patients were still included in the calculation of the incidence and point-prevalence for the concerned subtype of DEB. ‡Incidence (per million live births) = total no. of new patients born (1988–2018)/total no. of live births (1988–2018)\*1 000 000. Total live births in the Netherlands from 01-Jan-1988 until 31-Dec-2018: 5 830 469 (StatLine, CBS). §Point-prevalence (per million population) = total no. of patients alive at a time point (31-Dec-2018)/population at a time point (31-Dec-2018)\*1 000 000. Total Dutch population, 31-Dec-2018: 17 282 163 (StatLine, CBS). ¶The group of 'Unsolved' DEB-patients consisted of a family of three patients with DDEB-localized. ††In this patient the subtype of DDEB remained uncertain. †‡The group of 'Unsolved' RDEB-patients consisted of the following:  $n = 3$  RDEB-intermediate and  $n = 1$  RDEB-severe (in all patients one pathogenic mutation in COL7A1 could be found). §§The group of 'No DNA' RDEB-patients consisted of the following:  $n = 2$  RDEB-severe (both deceased patients were included in the calculation of the average age at death for RDEB-severe) and  $n = 1$  RDEB-intermediate.

EB type	Cleavage level	Inheritance	Subtype	Gene affected	No. of affected patients (families)	Average age of patients (alive) on 31-Dec-2018 (in years) <sup>†</sup>	Incidence <sup>1,2</sup> DEB subtype	Point-prevalence <sup>1,3</sup> DEB subtype
DEB	Sub-lamina densa	Dominant	Localized		53 (28)	33.2	4.3	3.2
			Intermediate		41 (16)	32.7	3.8	2.3
			Pruriginosa		4 (3)	39.0	-	0.2
			Self-improving		1 (1)	1.4	0.2	8.6
			Unknown		4 (3)	-	-	0.1
			Unsolved <sup>‡</sup>		3 (1)	-	-	-
			No DNA <sup>§</sup>		1 (1)	-	-	-
		Recessive	Localized	COL7A1	5 (5)	52.9	0.3	0.3
			Intermediate		15 (14)	23.7	2.2	1.0
			Severe		19 (18)	21.9	2.4	0.5
			Inversa		7 (6)	29.9	0.5	5.5
			Unsolved <sup>¶</sup>		4 (3)	-	-	2.1
Total DEB		Unknown	No DNA <sup>‡</sup>		3 (3)	-	-	-
					1 (1)	-	-	-
					161 (103)	32.5 years	14.1	8.3

DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa.



**Table 4** Epidemiological data and distribution of Kindler Epidermolysis Bullosa in the Netherlands for the time period 1988–2018,  $n = 4$ †In two patients no pathogenic mutation(s) could be found. Those patients were still included in the calculation of the incidence and point-prevalence of Kindler EB. ‡Incidence (per million) = total no. of new Kindler EB-patients born (1988–2018)/total no. of live births (1988–2018)\*1 000 000. Total live births in the Netherlands from 01-Jan-1988 until 31-Dec-2018: 5 830 469 (Statline, CBS). §Point-prevalence (per million) = total no. of Kindler EB-patients alive at a time point (31-Dec-2018)/population at a time point (31-Dec-2018)\*1 000 000. Total Dutch population, 31-Dec-2018: 17 282 163 (Statline, CBS).

EB type	Cleavage level	Inheritance	Gene affected	No. of affected patients (families)	Average age of patients (alive) on 31-Dec-2018	Incidence <sup>‡</sup>	Point-prevalence <sup>§</sup>
Kindler EB	Mixed	Recessive	FERMT1	2 (2)	13.8 years	0.5	0.2
			Unsolved	2 (2)			

EB, epidermolysis bullosa; Kindler EB, Kindler epidermolysis bullosa.

53 patients (49 families; 32.9%), of which 35.8% carried a homozygous mutation (94.7% of which had consanguineous parents). In 7.5% of the DEB-patients ( $n = 12$ ) the genotype remained unknown.

**Kindler EB** Kindler EB was diagnosed in only four patients (four families; 0.9%) with an incidence of 0.5 per million live births and a point-prevalence of 0.2 per million population (Figs. 1 and 2a, Table 4). In two patients with Kindler EB compound heterozygous mutations in *FERMT1* were found, in the remaining two patients a clinical phenotype of Kindler EB was present, but no pathogenic mutations could be found.

**Epidemiological trends** Based on the increasing number of registered EB-patients at our centre, the point-prevalence of EBS and DEB has progressively increased over the years, while it plateaued for JEB after an initial period of increase (Fig. 1a). On the other hand, the yearly incidence rates showed a fluctuating pattern (Fig. 1b).

### EB and mortality

For the Netherlands, the average life expectancy was 81.8 years (80.2 years for males and 83.3 years for females; 31-Dec-2018, StatLine, CBS). During the investigated time period, 73 EB-patients (15.7%) in the Dutch-EB-Reg died, with an average age at death (AAD) of 22.9 years ( $n = 72$ ; SD: 31.0;  $n = 1$  AAD unknown). Of the 73 deceased EB-patients, 68 patients had a recessive type of EB (47 JEB-patients, 16 DEB-patients, four EBS-patients and one patient with Kindler EB) and five patients a dominant type. A total of 53 patients with recessive EB (77.9%) died as a direct consequence of known complications of their EB; 72.6% of the total group of 73 deceased EB-patients. In another six patients with recessive EB it was not possible to find out whether their death was related to EB (8.8%). The remaining nine patients with recessive EB died from EB-unrelated causes (13.2%), which was also true for the five patients with dominant EB (Table 5).

**Mortality and EBS** The average age of the alive EBS-patients in the Dutch-EB-Reg was 34.3 years ( $n = 205$ ; SD: 20.9) (31-Dec-2018). Seven EBS-patients died during the investigated time period. Two patients with REBS-muscular dystrophy died at the age of 43.7 and 46.0 years from cardiac failure. Two other patients with REBS died at the age of 88.6 and 82.3 years, both considered being EB-unrelated. Three patients with dominant EBS died at the age of 83.9, 67.3 and 23.8 years, all three considered being EB-unrelated (Tables 1 and 5).

**Mortality and JEB** The average age of the alive JEB-patients in the Dutch-EB-Reg was 33.0 years ( $n = 36$ ; SD: 24.3) (31-Dec-2018). A total of 47 JEB-patients died during the investigated time period (excluding two stillbirths with an unknown subtype

**Table 5** Mortality data of each major type and subtype of Epidermolysis Bullosa in the Netherlands for the time period 1988–2018,  $n = 73$ †Excluding two stillbirths with an unknown subtype of JEB, an induced partus of a fetus with JEB-severe and a patient with JEB-severe who died before 1988 but was captured in the Dutch-EB-Reg during the investigated time period. ‡Every cause of death other than 'unknown' or 'EB-unrelated' are considered to be EB-related. §In one patient with JEB-intermediate the age at death remained unknown ( $n = 72$ ).

EB (subtype)	Gene affected	No. of deceased patients <sup>1</sup>	Cause of death <sup>2</sup>	Age at death (average) <sup>3</sup>
EBS	Localized Intermediate Ogna	1 1 1	EB-unrelated ( $n = 3$ )	83.9 y 58.4 y (SD 31.1)
	PLEC1	2		45.6 y
REBS	Muscular dystrophy	2	Cardiac failure ( $n = 2$ )	44.9 y
	Severe	2	EB-unrelated ( $n = 2$ )	65.2 y (SD 23.6)
JEB	Intermediate LAMA3 COL17A1 ITGB4	4 3 4 1	Euthanasia; chronic ulcers ( $n = 1$ ) Respiratory infection ( $n = 1$ ) EB-unrelated ( $n = 2$ ) Unknown ( $n = 2$ ) EB-unrelated ( $n = 1$ ) (Metastatic) SCC ( $n = 1$ ) EB-unrelated ( $n = 3$ ) Unknown ( $n = 1$ )	55.9 y (SD 35.0) 83.4 y (SD 7.0) 62.8 y (SD 25.4) 53.0 y (SD 15.2) 65.6 y
	Severe	21	Failure to thrive ( $n = 11$ ) Respiratory insufficiency ( $n = 4$ ) Gastro-enteritis ( $n = 2$ ) Sepsis ( $n = 2$ ) Pneumonia ( $n = 1$ ) Euthanasia ( $n = 1$ )	5.4 m (SD 7.5)
	LAMC2	3	Failure to thrive ( $n = 2$ ) Respiratory insufficiency ( $n = 1$ )	2.7 m (SD 0.6)
	LAMA3	2	Gastro-enteritis ( $n = 1$ ) Sepsis ( $n = 1$ )	4.7 m
	No DNA	3	Failure to thrive ( $n = 1$ ) Pneumonia ( $n = 1$ ) Unknown ( $n = 1$ )	1.9 m (SD 2.0)
	Pyloric atresia	2 1 2 1	(Cardio)respiratory insufficiency ( $n = 6$ )	6 d (SD 2.3)
	ITGB4	2		
	ITGA6	1		
	Unsolved	2		
	No DNA	1		
DEB	Localized	1	EB-unrelated ( $n = 2$ )	54.3 y
	Intermediate	1		89.4 y
	Severe	2	Sepsis; stem cell Tx ( $n = 1$ ) Palliative treatment ( $n = 1$ )	7.1 y
RDEB	COL7A1	2	(Metastatic) SCC ( $n = 4$ ) Cardiac failure ( $n = 3$ ) Abstinence ( $n = 2$ ) Euthanasia ( $n = 1$ ) Sepsis; chronic wounds ( $n = 1$ ) Unknown ( $n = 1$ )	18.5 y (SD 14.2) 18.8 y (SD 16.7)
	COL7A1	4		
	Severe	3		
	Intermediate	2		
	COL7A1	2		
	Severe	4		
	COL7A1	3		
	Intermediate	2		
	COL7A1	1		
	No DNA	2		
	Inversa	2	Sepsis ( $n = 1$ ) EB-unrelated ( $n = 1$ )	32.6 y
Kindler EB	FERMT1	1	Unknown ( $n = 1$ )	67.7 y
Total EB		73	72.6% EB-related	22.9 years (SD 31.0)

EB, epidermolysis bullosa; EBS, epidermolysis bullosa simplex; DDEB, dominant dystrophic epidermolysis bullosa; DEB, dystrophic epidermolysis bullosa; JEB, junctional epidermolysis bullosa; Kindler EB, Kindler epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa; REBS, recessive epidermolysis bullosa simplex; SCC, squamous cell carcinoma; SD, standard deviation.

of JEB, an induced partus of a foetus with JEB-severe and a patient with JEB-severe who died before 1988 but was captured in the Dutch-EB-Reg during the investigated time period). For JEB-pyloric atresia an AAD of 6 days was calculated ( $n = 6$ ; SD: 2.3). All of whom died shortly after (cardio)respiratory problems occurred and an abstaining policy was initiated. For JEB-severe an AAD of 4.7 months ( $n = 29$ ; SD: 6.5) was calculated, with an exceptional outlier of 2.7 years, of which 26 patients (90%) died within the first year of life. All patients with JEB-severe died from EB-related complications, in order of frequency: failure to thrive, respiratory insufficiency, infectious diseases and euthanasia ( $n = 1$  unknown). For JEB-intermediate an AAD of 62.8 years ( $n = 11$ ; SD: 25.4) was calculated. Those patients died from: infectious diseases, euthanasia, metastatic squamous cell carcinoma and EB-unrelated causes ( $n = 3$  unknown) (Table 5).

**Mortality and DEB** The average age of the alive DEB-patients in the Dutch-EB-Reg was 32.5 years ( $n = 143$ ; SD: 23.0) (31-Dec-2018), divided into an average age of 28.8 years for patients with RDEB ( $n = 37$ ; SD: 20.7) and 33.3 years for patients with DDEB ( $n = 105$ ; SD: 23.5). A total of 16 RDEB-patients died during the investigated time period with an average AAD of 18.8 years (SD: 16.7), further subdivided into an average AAD of 18.5 years for RDEB-severe ( $n = 12$ ; SD: 14.2). All RDEB-severe patients died from EB-related complications: (metastatic) SCC, cardiac failure, abstinence, euthanasia and sepsis ( $n = 1$  unknown). Two patients with RDEB-intermediate died during the investigated time period at a young age from EB-related complications (AAD 8.4 months and 13.5 years). Two patients with RDEB-inversa died during the investigated time period at the age of 8.0 and 57.3 years, from sepsis caused by chronic wounds and an EB-unrelated cause, respectively. Both patients with DDEB died from EB-unrelated causes (AAD of 54.3 and 89.4 years; Table 5).

**Mortality and Kindler EB** One patient with Kindler EB died during the investigated time period at the age of 67.7 years. The cause of death remained unknown and therefore a potential correlation with EB uncertain (Table 5). The other patients with Kindler EB in the Dutch-EB-Reg were still alive, with an average age of 13.8 years ( $n = 3$ ; SD 9.3) (31-Dec-2018) (Table 4).

## Discussion

### Point-prevalence and incidence

This observational study presents epidemiological data on each subtype of EB, extracted from the molecularly well-characterized Dutch EB cohort in the Dutch-EB-Reg. In recent decades, several epidemiological studies have been carried out in different countries, reporting varying and sometimes inconclusive incidences and prevalences (1.4–25.0 per million live births and 2.82–54.0 per million population, respectively), mostly based on clinical features or molecular findings.<sup>6–19</sup> In 90.5% of the EB-

patients in our cohort the diagnosis was genetically confirmed, allowing accurate epidemiological analyses.

Both the calculated incidence of 41.3 per million live births and point-prevalence of 22.4 per million population are high compared to that reported in other countries, especially if the 26 patients with an EB-related skin fragility disorder would be included (incidence of 44.9 per million live births; point-prevalence of 23.7 per million population) (Fig. 1, Table S1, Supporting Information). Over the years, increased knowledge, advanced diagnostics and the reputation of our centre ensured that an increasing number of EB-patients were seen at our centre and captured in the Dutch-EB-Reg. The well-organized set-up in a small and highly populated country, a robust healthcare system with a good insurance policy and collaboration between specialists in the Netherlands ensured that most EB-patients were referred to our centre (near-complete ascertainment), especially those with severe subtypes of EB. Furthermore, being the only national expertise centre for EB, all mutation analysis for EB takes place in the UMCG. Therefore, we believe that the Dutch-EB-Reg documents most of the EB-patients in the Dutch population and our calculated figures come close to the actual numbers, even though they are higher than previously reported. Our epidemiological data from the well-characterized Dutch EB cohort thus indicate that EB may be more common than considered so far.

### Risk of underestimation

Despite the expertise, knowledge and reputation of our centre, it is assumed that still not every patient is referred to our national centre, especially those with rather mild subtypes of EB. Those patients may be treated by their general practitioner or local specialist, as earlier noticed by Horn *et al.*<sup>14</sup> Besides, patients with milder subtypes of EB who were born in the last few years are expected to be registered in the following years, especially in case of late-onset EB. Given the increasing number of registered patients at our centre, the calculated figures might therefore still be an underestimation.

### Risk of misclassification

Another strength of our Dutch-EB-Reg is the long period of systematic data collection and longitudinal follow-up. During the investigated time period, significant efforts were made to adequately monitor the patient records and identify affected family members. Despite the high level of expertise of our centre, patients may have been misclassified. However, this number is expected to be low, as in more than ninety per cent of the patients the diagnosis was genetically confirmed (Fig. 2). In the group of 'Unsolved' patients ( $n = 22$ ) DNA analysis could not provide a genetic diagnosis using the gold standard techniques at the time of visiting our centre, neither with Sanger sequencing nor with a panel of multiple EB-related genes. This may be due to technical shortcomings, because the diagnosis of EB is

incorrect, the presence of unusual mutations or mutations in genes not known at the time of diagnostics, or mutations in as yet unknown genes. Over the years developments have been made in the registration and (sub)classification of the different subtypes of EB. Although we have made attempts to correctly convert the diagnoses from earlier consensus classifications to the latest, these changes may have led to misclassifications and fluctuating incidences and prevalences over time. This may be particularly true for EBS, as the EB-related skin fragility disorders were previously included in the EB spectrum as suprabasal EBS (Fig. 1, Table S1, Supporting Information).<sup>1</sup>

### Distribution of EB subtypes

The distribution of the subtypes of EB in the Dutch-EB-Reg (EBS 45.7%, JEB 18.8%, DEB 34.7% (DDEB 23.1% and RDEB 11.4%) and Kindler EB 0.9%) differ from those reported in other countries.<sup>6,7,16,20–22</sup> Noteworthy, the population of JEB-patients in the Dutch-EB-Reg is relatively higher than reported in other countries. Worldwide variations in the population and level of immigration (e.g. ethnic background, consanguineous marriages, spectrum of mutations) may affect the epidemiology and distribution of the subtypes of EB per region.<sup>20,23,24</sup> During the investigated time period, the Netherlands received an increasing number of immigrants, especially from countries where consanguineous marriages are more common than in the native Dutch population (StatLine, CBS), which may have resulted in an increasing number of patients with recessive, and usually more severe, subtypes of EB.

### Epidemiological trends

Over the years, the point-prevalence of EB, particularly EBS and DEB, has progressively increased, representing an increasing number of registered EB-patients at our centre. Interestingly, the point-prevalence of JEB has reached a plateau since 2014. This may be attributed to the fact that the point-prevalence of JEB mainly consists of the non-lethal JEB-subtypes, as the average life expectancy of patients with JEB-severe and JEB-PA in the Dutch-EB-Reg was 4.7 months and 6 days, respectively. Apparently, we have been able to register all other JEB-patients in the Dutch-EB-Reg, in contrast to the relatively milder and more common EBS and DDEB. Over the years, the annual incidence rates showed a fluctuating pattern. The high incidence of EBS in 2011 is likely a chance finding, all patients were crosschecked.

### EB and mortality

We found that 72.6% of the deceased EB-patients died as a direct consequence of EB-related complications. JEB-patients experienced the highest mortality rate, with an average survival of 6 days for JEB-pyloric atresia ( $n = 6$ ), 4.7 months for JEB-severe ( $n = 29$ ) and 62.8 years for JEB-intermediate ( $n = 12$ ). The AAD of patients with JEB-pyloric atresia and JEB-severe in

the Dutch-EB-Reg is low in comparison with other studies.<sup>10,25</sup> The deceased patients with RDEB-severe had an average AAD of 18.5 years ( $n = 12$ ), lower than the earlier reported 29.4 years ( $n = 4$ ) by Kho *et al.*<sup>10</sup> However, due to the relatively small number of deceased RDEB-patients in both the Dutch-EB-Reg (with high standard deviations) and other studies, and the young age of the alive RDEB-patients in the Dutch cohort, the question is whether these data are comparable and representative for the whole RDEB population. Future studies have to show whether the life expectancy of RDEB-severe patients is truly that low.

### Foreign EB-patients referred to our expertise centre

Since the referral of the first EB-patients from Belgium in 1997, an increasing number of EB-patients were referred to our centre by specialists from foreign countries for diagnostic testing and/or to receive medical care. This demonstrates the need and value of cross-country collaboration of healthcare professionals in the diagnosis and care of EB-patients and rare diseases in general, which might be impossible to organize for each disease in each country individually, and from which the patients can only benefit.

### Conclusion

This study shows that EB might be more common than assumed before and emphasizes the importance of thorough reporting systems and registries worldwide, which is invaluable for the design and execution of (upcoming) therapeutic trials. Besides, it provides an insight into the extensive need for (specialized) medical care of EB-patients.

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### Ethical approval

This study contains routinely collected healthcare data.

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### Supporting information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Distribution of the genes involved in patients with an EB-related skin fragility disorder in the Dutch Epidermolysis Bullosa Registry for the time period 1988–2018,  $n = 26$ .

**Table S1.** Epidemiological data and distribution of EB-related skin fragility disorders in the Netherlands for the time period 1988–2018,  $n = 26$ .

**Appendix S1.** Epidemiological data on EB-related skin fragility disorders from the Dutch EB Registry.